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THE INFLUENCE OF ALCOHOL, ETHER, AND CHLOROFORM ON NATURAL IMMUNITY IN ITS RELATION TO LEUCOCYTOSIS AND PHAGOCYTOSIS.*

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THE presence of pathogenic bacteria in perfectly healthy individuals has been repeatedly demonstrated by various observers. The bacillus of tuberculosis, the diplococcus of Fränkel, or the Klebs-Löffler bacillus may be present in the air passages of persons who are not in the least inconvenienced thereby, and do not betray the slightest signs of tuberculosis, pneumonia, or diphtheria. The streptococcus and the various pyogenic staphylococci may be present in the skin or the mucous lining of various orifices of the body without giving rise to any symptoms whatsoever. But at some moment, under certain conditions or in a certain environment, these very organisms, which hitherto had seemed harmless, may suddenly become active, multiply rapidly, and produce a disease that entails serious and even fatal consequences. In this work I have tried to study certain factors that weaken the natural resistance or immunity and allow germs to attack the body.

Before the discovery of the pneumococcus it was thought that cold was the principal cause of fibrinous pneumonia. This led Heidenhain to make some experiments on rabbits. He tried to chill them suddenly by removing them from a hot into a cold atmosphere, but failed to produce pneumonia. Though these animals are not prone to that affection, still, had the specific organism been present, the experiments might have come out differently.

At the present time cold is regarded as only a predisposing cause, or, as Eichhorst calls it, *ein Hilfsmoment für die Infection.* We also know that alcoholism is a predisposing cause, and, if alcohol, why not ether and chloroform, in view of post-operative

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*Received for Publication March 16, 1904.

pneumonia and other infections in apparently aseptic cases? It is the influence of alcohol, ether, and chloroform on natural immunity, and especially on the rôle that the leucocytes play in the defense of the organism against various infections that I have studied.

A good deal of work has been done along the same lines, the most recent being that of Snel, who, at the suggestion of Talma, carried out a number of experiments with guinea pigs, relative to the effect of ether, alcohol, and chloral on immunity. He found that those agents suspend immunity temporarily; and, further, that the longer the period of anesthesia, the shorter the process of infection. Snel employed the anthrax bacillus as the infectious material, and in every instance the infection proved fatal to animals, otherwise immune, when they were subjected to narcotics.

Platania—as quoted by Snel—obtained as early as 1889 similar results in frogs, with curare, which he found reduced their resisting power against Bacillus anthracis.

Cantacuzène demonstrated the detrimental effects of opium on leucocytes. He observed that guinea-pigs, well immunized against typhoid, when narcotized with opium succumbed readily to typhoid infection. It was observed that the phagocytes did not intervene as promptly as in the cases where opium was not used. Oppel confirmed the results of Cantacuzène by similar experiments. Gheorghiewski, quoted by Metchnikoff, obtained identical results in his experiments with tincture of opium in guinea-pigs. He also found that diapedesis and phagocytosis were impaired; the movements and tactile sensibility were greatly diminished. The animals that were narcotized, though thoroughly immunized, died regularly from the infection, owing, it seemed, to the delayed phagocytosis, in consequence of which the microbes were not destroyed in time.

The ingenious experiments of Besredka show distinctly the rôle which the leucocytes play in defending the organism against poisons. He injected trisulphide of arsenic (which is insoluble and easily recognized as bright orange-colored granules) into the peritoneal cavity of guinea-pigs. This at first caused a disappearance of the leucocytes, followed later by a hyperleucocytosis with predominance of macrophages, which were the principal cells to take up the orange-colored granules of the trisulphide of arsenic. In another experiment he first induced artificially a hyperleucocytosis in the peritoneal cavity, and then injected a lethal dose of the trisulphide, but as in the first experiment, the granules were taken up promptly by the macrophages, and the animal remained unharmed.

In another interesting experiment Besredka demonstrated the capability of the phagocytes to select materials. He injected into the peritoneal cavity trisulphide of arsenic and carmine at the same time, and found that, while a few leucocytes here and there contained orange-colored granules, many of them contained carmine granules. The same phenomenon occurred even when he injected the carmine some time after the arsenic.

My own experiments, begun in 1902, are divided into three separate series, viz., those with alcohol, with ether, and with chloroform. The rabbit was selected as the most suitable animal, The narcotics were usually administered hypodermically, the alcohol and ether in pure form, while the chloroform was shaken up with an equal amount of distilled water, so as to render it less irritating. The average dose of alcohol and ether injected was 1.5–2 gr. to the kilogram of rabbit weight, and of chloroform 1 gr. per kilogram. That dose for alcohol and ether is perfectly safe. In twenty experiments I met with only a single accident, the needle entering a vein, so that ether and some air was injected. The rabbit died instantaneously. But chloroform is not so safe, especially in young animals. In one case two young rabbits succumbed almost immediately after the injection. The rabbits that recovered from the immediate effects of the narcotics all remained well. These experiments were all preliminary. The materials used for inoculation were cultures of pneumococcus and streptococcus.

ALCOHOL SERIES.

EXPERIMENT I.

August 17, 4 P. M.—Rabbit A: white; weight, 2 kg.; leucocytes, 8,600; temperature, 103°. Injected 1 c.c. of a fresh culture of streptococcus hypodermically in ear.

August 18, 4 P. M.—Leucocytes, 15,400; temperature, 101°.5.

August 19, 4 P. M.—Leucocytes, 23,300; temperature, 101°.4.

The rabbit remained well.

Rabbit B: white and black; weight 2 kg.; temperature, 103°; leucocytes, 8,800. Injected 4 c.c. of alcohol (95 per cent.) and 1 c.c. of streptococcus culture (same as Rabbit A).

August 18, 4 P. M.—Leucocytes, 7,000; temperature, 103°.

August 19, 4 P. M.—Leucocytes, 7,900; temperature, 103°.8.

Died in a cachetic state ten days after inoculation.

EXPERIMENT II.

August 28, 3 P. M.—Rabbit A: white; weight, 1 kg.; leucocytes, 14,000. Injected 1 c.c. of streptococcus culture.

August 29, 3 P. M.—Leucocytes, 15,000.

August 30, 3 P. M.—Leucocytes, 9,000.

August 31.—Died sixty hours after inoculation. Smears of heart's blood showed streptococci.

Rabbit B: gray; weight, 1 kg.; leucocytes, 15,000. Received 2 c.c. of alcohol and 1 c.c. of culture. Died in twenty-four hours. Leucocytes one hour ante mortem, 5,500; streptococcus recovered by cultures; smears from blood were negative.

EXPERIMENT III.

August 31, 4 P. M.—Rabbit A: gray; weight, 1¼ kg.; leucocytes, 10,000; temperature, 102°.5. Injected 3 c.c. of alcohol and 1/40,000 c.c. of a pneumococcus culture.

September 1, 4 P. M.—Leucocytes, 10,600; temperature, 103°.5.

September 2, 4 P. M.—Leucocytes, 19,000; temperature, 103°.8.

September 3, 4 P. M.—Leucocytes, 14,000; temperature, 104°.

The number of leucocytes gradually decreased, and the rabbit died at the end of one week. The pneumococcus was found in smears.

Rabbit B: grayish yellow, weight, 1¼ kg.; temperature, 101°.5; leucocytes, 8,600. Received 1/40,000 c.c. pneumococcus culture.

September 1, 4 P. M.—Appeared less sick than Rabbit A. Temperature, 104°.6; leucocytes, 10,200.

September 2, 4 P. M.—Leucocytes, 18,700; temperature, 105°.

September 3, 4 P. M.—Leucocytes, 22,000; temperature, 105°.

The leucocyte count fell gradually, and the rabbit died at about the same time as Rabbit A.

EXPERIMENT IV.

September 7, 3 P. M.—Rabbit A: gray; weight, 1½ kg., temperature, 102°; leucocytes, 14,000. Received 3 c.c. of alcohol and 0.5 c.c. of pneumococcus culture intraperitoneally. The rabbit died during the night—time unknown. The pneumococcus was found in smears.

Rabbit B: gray; weight 1½ kg.; temperature 102°; leucocytes, 14,600. Received 0.5 c.c. of pneumococcus culture. Died during the night. Diplococcus pneumoniae was found in smears.

EXPERIMENT V.

September 10, 3 p. m.—Rabbit A: black and white; weight, 1½ kg.; temperature, 101°.5; leucocytes, 14,000. Injected 3 c.c. of alcohol and 1 c.c. of pneumococcus culture. Died in 22 hours. Leucocytes immediately post mortem, 1,100. An abundance of Diplococcus pneumoniae was found in smears.

Rabbit B: black; weight, 2 kg.; temperature, 102°; leucocytes, 10,500. Received 1⅓ c.c. of pneumococcus culture.

September 11, 5 p. m.—Temperature, 104°; leucocytes, 12,400.

September 12, 5 p. m.—Temperature, 104°; leucocytes, 11,400.

September 13, 4 p. m.—Temperature, 103°.5; leucocytes, 18,000.

Rabbit recovered.

EXPERIMENT VI.

September 23, 3 p. m.—Rabbit A: gray; weight 1¾ kg.; temperature, 102°; leucocytes, 8,400. Received 3½ c.c. of alcohol and 1 c.c. of streptococcus (48-hour culture).

September 24, 4 p. m.—Temperature, 105°; leucocytes, 6,800.

September 25, 4 p. m.—Temperature, 107°.2; leucocytes, 2,000.

Died during the night of September 25.

Rabbit B: gray-white; weight, 1¾ kg.; temperature, 102°.5; leucocytes, 7,700. Received 1 c.c. of streptococcus culture (48-hour).

September 24, 4 p. m.—Temperature, 105°; leucocytes, 10,300.

September 25, 4 p. m.—Temperature, 104°.8; leucocytes, 12,600.

September 26, 4 p. m.—Temperature, 105°; leucocytes, 21,300.

The rabbit remained well.

EXPERIMENT VII.

October 2, 4 p. m.—Rabbit A: gray; weight, 1½ kg.; temperature 102°; leucocytes, 10,200. Received 3 c.c. of alcohol and 1¾ c.c. of pneumococcus culture.

October 3, 4 p. m.—Temperature, 105°; leucocytes, 5,300.

October 5.—Died about 1 p. m. Leucocytes ante mortem 7,700. The pneumococcus was found in cultures.

Rabbit B: white; weight, 1½ kg.; temperature, 101°.8; leucocytes 9,200. Received 1¾ c.c. of pneumococcus culture.

October 3, 4 p. m.—Temperature, 106°.2; leucocytes, 11,300.

October 5, 4 p. m.—Temperature, 105°; leucocytes, 24,000.

October 6.—Died 11 a. m. Leucocytes ante mortem 12,700. At autopsy peritonitis and multiple abscesses of the liver were found. The pneumococcus was found in smears and cultures.

EXPERIMENT VIII.

October 5, 4 p. m.—Rabbit A: gray; weight, 1½ kg.; temperature, 102°; leucocytes, 11,200. Injected 3 c.c. of alcohol and 3 c.c. of diluted pneumococcic blood from Rabbit A, Experiment VII.

October 6.—Died fifteen hours after inoculation. Leucocytes immediately post mortem, 1,800.

Rabbit B: black; weight, 1½ kg.; temperature, 102°.5; leucocytes, 9,800. Received the same pneumococcic blood as Rabbit A.

October 6, 4 P. M.—Temperature, 106°.6; leucocytes, 22,000.

October 7, 4 P. M.—Died 3 P. M. Leucocytes post mortem (heart's blood), 11,300.

Pneumococci were found in both rabbits.

EXPERIMENT IX.

October 9, 4 P. M.—Rabbit A: black and white; weight, 1½ kg.; temperature, 101°.5; leucocytes, 11,800. Received 2 c.c. of alcohol and 1½ c.c. (two loops in salt solution) of pneumococcus culture.

October 10, 4 P. M.—Temperature, 105°; leucocytes, 2,400.

October 11.—Died thirty hours after inoculation.

Cultures gave positive results.

Rabbit B: white; weight, 1½ kg.; temperature, 102°; leucocytes, 9,600. Received 2½ c.c. of same mixture of pneumococcus in salt solution as Rabbit A, but this rabbit received 0.5 c.c. more than Rabbit A, owing to error in technique.

October 10, 4 P. M.—Temperature 104°.5; leucocytes, 11,100.

October 11.—Died forty-two hours after inoculation.

In spite of the larger dose of culture received, Rabbit B survived his fellow by 12 hours. Pneumococci were found in the cultures.

EXPERIMENT X.

October 14, 4 P. M.—Rabbit A: gray; weight, 2 kg.; temperature, 101°; leucocytes, 10,900. Received 4 c.c. of alcohol and 2 c.c. of pneumococcus culture.

October 15, 4 P. M.—Temperature 103°.5; leucocytes, 24,000.

October 16, 4 P. M.—Temperature 105°; leucocytes, 5,700. Rabbit appeared quite sick.

October 17, 4 P. M.—Temperature, 105°; leucocytes, 3,700.

October 18.—Died at 11 A. M.

Smears of blood showed an abundance of pneumococci.

Rabbit B: white; weight 1¾ kg.; temperature, 100°; leucocytes, 12,000. Received 2 c.c. of same culture as Rabbit A.

October 15, 4 P. M.—Temperature, 103°.5; leucocytes, 16,000.

October 16, 4 P. M.—Temperature, 103°.6; leucocytes, 25,400.

October 17, 4 P. M.—Temperature, 103°; leucocytes, 27,000.

October 18.—Apparently well.

October 19.—Continued to be well. Recovered.

The following conclusions may be drawn from the foregoing experiments:

That eight out of the ten experiments were positive is ample evidence that alcohol has a detrimental influence upon the resisting power of the animals. The results in Experiments I, IV, V, and X are striking. Every narcotized animal succumbed to the infection, while all of the control animals completely recovered. In Experiments II, VII, VIII, and IX we see that every control rabbit survived his alcoholized fellow for a certain space of time. And the controls exhibited other signs of resistance; *e. g.*, higher leucocytic counts and better physical signs.

The average leucocytosis of the control animals is markedly greater than that of the narcotized ones. In every instance where the leucocyte count rose considerably above the initial number soon after the infection, and remained high for forty-eight or seventy-two hours, the animal recovered, or at least it remained alive for a variable space of time. But in those animals where the leucocytes did not show a tendency to rise above the initial number, or where they rose for a short time and then fell rapidly, and especially when it fell below the initial count, the animals succumbed.

The relation between the number of leucocytes and the bacteria circulating in the blood will be shown later in the study.

ETHER SERIES.

EXPERIMENT I.

May 25, 4 P. M.—Rabbit A (Belgian hare): weight, 3 kg.; temperature, 101°; leucocytes, 12,000. Received 5 c.c. of ether and 1 c.c. of attenuated pneumococcus culture intratracheally.

May 26, 4 P. M.—Breathing very rapidly; very sick. Temperature, 104°.5; leucocytes, 13,500.

May 27.—Died thirty hours after inoculation.

Post-mortem: Both lungs very edematous; left lung grayish in appearance, and floats. Smears of heart's blood show an abundance of pneumococci.

Rabbit B (Belgian hare): weight, 2 kg.; temperature, 101°.8; leucocytes; 9,500. Received 1 c.c. of same culture as A intratracheally.

May 26, 4 P. M.—Temperature, 105°.5; leucocytes, 16,000.

May 27, 4 P. M.—Temperature, 104°.8; leucocytes, 19,300.

May 28, 4 P. M.—Temperature, 105°.4; leucocytes, 33,600.

May 29, 4 P. M.—Temperature, 102°.5; leucocytes, 18,600.

Recovered.

EXPERIMENT II.

June 5, 3 P. M.—Rabbit A: weight, 2 kg.; temperature, 102°; leucocytes, 11,000. Received 3½ c.c. of ether and 2 c.c. of streptococcus culture of medium virulence.

June 6, 4 P. M.—Temperature, 106°; leucocytes, 16,000.

June 7, 4 P. M.—Temperature, 104°; leucocytes, 6,400.

June 8.—Found dead early in the morning. Cultures made from the blood gave positive results.

Rabbit B (Belgian hare): weight, 2 kg.; temperature, 101°8; leucocytes, 9,800. Received same culture as A (2 c.c.).

June 6, 4 P. M.—Temperature, 104°; leucocytes, 18,000.

June 7, 4 P. M.—Temperature, 104°5; leucocytes, 30,000.

June 8, 4 P. M.—Temperature, 105°2; leucocytes, 32,000.

June 9, 4 P. M.—Temperature, 103°5; leucocytes, 26,000.

The rabbit developed a local abscess, but remained well otherwise.

EXPERIMENT III.

June 11, 4 P. M.—Rabbit A (Belgian hare): weight, 2 kg.; temperature, 102°; leucocytes, 8,500. Received 4 c.c. of ether and 1 c.c. of a streptococcus culture.

June 12, 4 P. M.—Temperature, 102°; leucocytes, 8,000.

June 13, 4 P. M.—Temperature, 103°; leucocytes, 16,000.

June 15, 4 P. M.—Temperature, 102°5; leucocytes, 8,200.

June 16, 4 P. M.—Temperature, 103°; leucocytes, 7,100.

June 17, 4 P. M.—Temperature, 103°; leucocytes, 7,200.

June 18.—Died early in the morning; streptococcus found abundantly in blood.

Rabbit B (Belgian hare): weight, 2¼ kg.; temperature, 103°; leucocytes, 8,300. Received 1 c.c. of same culture as A.

June 12, 4 P. M.—Temperature, 103°5; leucocytes, 9,000.

June 13, 4 P. M.—Temperature, 103°5; leucocytes, 11,000.

June 15, 4 P. M.—Temperature, 104°5; leucocytes, 14,000.

June 16, 4 P. M.—Temperature, 104°; leucocytes, 14,600.

June 17, 4 P. M.—Temperature, 103°5; leucocytes, 11,000.

Rabbit remained well.

EXPERIMENT IV.

June 25, 4 P. M.—Rabbit A: weight, 1½ kg.; temperature, 103°; leucocytes, 10,500. Received 3 c.c. of ether and 1 c.c. of pneumococcus culture intratracheally.

June 26, 3 P. M.—Temperature, 101°6; leucocytes, 9,300.

June 27, 4 P. M.—Temperature, 102°; leucocytes, 7,500.

June 28.—Found dead in morning. Autopsy: lung edematous; infarct in left lower lobe; areas of acute congestion; pneumococcus present in smears.

Rabbit B: weight, 1¾ kg.; temperature, 102°5; leucocytes, 14,600. Received 1 c.c. of same culture as A, intratracheally.

June 26, 3 P. M.—Temperature, 105°2; leucocytes, 19,600.

June 27, 4 P. M.—Temperature, 103°5; leucocytes, 14,000.

June 29, 4 P. M.—Temperature, 103°; leucocytes, 17,000.

Died July 8. Examination for pneumococci in blood gave negative results. Lung edematous; no congestion.

EXPERIMENT V.

July 16, 3 P. M.—Rabbit A: weight, 2 kg.; temperature, 102°.6; leucocytes, 9,800. Injected 4 c.c. of ether and 3 c.c. of pneumococcus culture intravenously. Died eight hours after inoculation. Pneumococci present in blood (smears).

Rabbit B: weight, 2 kg.; temperature, 102°; leucocytes, 11,800. Received 3 c.c. of same culture intravenously. Died fifteen hours later. Bacteriologic examination gave positive results.

EXPERIMENT VI.

July 20, 3 P. M.—Rabbit A: weight, 2½ kg.; temperature, 102°.4; leucocytes, 10,500. Received 5 c.c. of ether and culture of pneumococcus intratracheally.

July 21, 3 P. M.—Temperature, 104°.6; leucocytes, 8,000.

July 22.—Died early in the morning. Smears from heart's blood showed pneumococcus with well-defined capsules.

Rabbit B: weight, 3 kg.; temperature 103°; leucocytes, 11,000. Received in the trachea same culture (No. 100) as Rabbit A.

July 21, 3 P. M.—Temperature, 104°; leucocytes, 18,000.

July 22, 3 P. M.—Temperature, 106°.5; leucocytes, 34,000.

July 23, 3 P. M.—Temperature, 104°.6; leucocytes, 22,000.

The rabbit recovered.

EXPERIMENT VII.

July 22, 4 P. M.—Rabbit A: weight, 3¼ kg.; temperature, 102°.5; leucocytes, 12,000. Received 6 c.c. of ether and 1 c.c. of pneumococcus culture hypodermically.

July 23, 4 P. M.—Temperature, 106°.5; leucocytes, 14,100.

July 24, 4 P. M.—Temperature, 107°; leucocytes, 15,000.

July 25, 4 P. M.—Temperature, 105°.5; leucocytes, 15,600.

Rabbit died August 1. No autopsy.

Rabbit B: weight, 2¼ kg.; temperature, 102°; leucocytes, 9,800. Received hypodermically 1 c.c. of same culture as A.

July 23, 4 P. M.—Temperature, 103°.8; leucocytes, 10,000.

July 24, 4 P. M.—Temperature, 102°; leucocytes, 11,000.

July 25.—Died in the morning. Pneumococci present in smears.

EXPERIMENT VIII.

July 27, 4 P. M.—Rabbit A: weight, 2 kg.; temperature, 101°.6; leucocytes, 11,500. Received 4 c.c. of ether and an intratracheal injection of 1 c.c. of pneumococcus culture.

July 28, 4 P. M.—Temperature, 106°.2; leucocytes, 5,000.

July 29.—Died during the day. Blood examination gave positive results. Lungs were edematous.

Rabbit B: weight, 2¼ kg.; temperature, 102°.5; leucocytes, 9,200. Ether inhalation for fifteen minutes; semiconsciousness. Received 1 c.c. of pneumococcus culture in the trachea.

July 28, 4 P. M.—Temperature, 104°5; leucocytes, 11,500.

July 29, 4 P. M.—Temperature, 104°5; leucocytes, 9,000.

Died August 2. Autopsy: Lungs edematous; serofibrinous peritonitis; pneumococcus present in exudate (cultures).

Rabbit C, control: weight, 2½ kg.; temperature, 101°5; leucocytes, 8,900. Received 1 c.c. of pneumococcus culture (same as A and B) in the trachea.

July 28, 4 P. M.—Temperature, 106°; leucocytes, 16,000.

July 29, 4 P. M.—Temperature, 105°5; leucocytes, 6,000.

July 30, 4 P. M.—Temperature, 102°; leucocytes, 7,200.

Died August 1. Pneumococcus present in smears.

EXPERIMENT IX.

July 30, 4 P. M.—Rabbit A: weight, 1 kg.; temperature, 102°; leucocytes, 13,000. Received 2 c.c. of ether and 0.5 c.c. of pneumococcus culture intratracheally. Died twelve hours later. Pneumococcus present in the blood.

Rabbit B: weight, 1 kg.; temperature, 101°8; leucocytes, 14,200. Ether by inhalation for 15 minutes and 0.5 c.c. of same culture as A intravenously. Died eighteen hours later. Pneumococci present in the blood.

Rabbit C: weight, 1 kg.; temperature, 102°5; leucocytes, 12,000. Received 0.5 c.c. of pneumococcus culture (same as A and B) intratracheally. Died about the same time as B. Pneumococci present.

EXPERIMENT X.

August 6, 9 A. M.—Rabbit A: weight, 1¾ kg.; temperature, 101°4; leucocytes, 12,000. Received 3.5 c.c. of ether and 1 c.c. pneumococcus culture intratracheally.

August 7, 9 A. M.—Temperature, 105°; leucocytes, 10,600.

August 8, 9 A. M.—Temperature, 105°5; leucocytes, 6,400.

Died August 9. Lung edematous and congested in areas. Pneumococci present in smears.

Rabbit B: weight, 1½ kg.; temperature, 102°; leucocytes, 9,500. Received 1 c.c. of pneumococci (same culture as A) in the trachea.

August 7, 9 A. M.—Temperature, 105°; leucocytes, 9,000.

August 8, 9 A. M.—Temperature, 106°; leucocytes, 18,200.

August 10, 4 P. M.—Temperature, 105°4; leucocytes, 40,000.

August 11, 4 P. M.—Temperature, 103°; leucocytes, 26,000.

The rabbit made a good recovery.

The foregoing experiments show that ether, administered in doses similar to those of alcohol, is still more positive in its effect. The difference in leucocytosis between the etherized rabbits and the controls is also more marked in the last than in the alcohol series.

In Experiment III, Rabbit B recovered with a maximum leucocytosis of 14,000 and an initial count of 8,300, while the narcotized rabbit (A), with a similar initial count and a leucocytosis on the second day of 16,000 (which, however, fell rapidly), died. One might presume from this result that, if Rabbit A, with a leucocytosis of 16,000 and infected with the same dose of culture as Rabbit B with a leucocytosis of only 14,000, died, while the latter completely recovered, the narcotic has not only a detrimental effect upon the leucocytes numerically, but that it also affects their function.

In Experiment VII, Rabbit A, narcotized, weighed $3\frac{1}{4}$ kg.—a very powerful animal. Although it received the usual dose of ether, it was not completely narcotized. The control weighed only $2\frac{1}{4}$ kg.—a difference of 1 kg.—but they received an equal dose of culture. This test was undertaken purposely, because, had the experiment turned out differently, its value would have been increased.

CHLOROFORM SERIES.

EXPERIMENT I.

October 21.—Rabbit A: weight, 2 kg.; temperature, 102°; leucocytes, 7,000. Received 2.5 c.c. of chloroform and 1.5 c.c. of a 48-hour streptococcus culture hypodermically in ear. Died the following night. Streptococcus found in blood.

Rabbit B: weight, 2 kg.; temperature, 102°.5; leucocytes, 8,200. Received 1.5 c.c. of same culture as A.

October 22, 4 P. M.—Temperature, 105°; leucocytes, 13,200.

October 23, 4 P. M.—Temperature, 106°; leucocytes, 12,900.

October 24, 4 P. M.—Temperature, 105°.5; leucocytes, 23,000.

Rabbit recovered.

EXPERIMENT II.

October 26, 4 P. M.—Rabbit A: weight, $1\frac{3}{4}$ kg.; temperature, 102°.5; leucocytes, 14,200. Kept under chloroform for thirty minutes. Received 2.5 c.c. of streptococcus culture subcutaneously in ear.

October 27, 4 P. M.—Temperature, 105°.5; leucocytes, 7,400.

October 28.—Died in the morning. Autopsy: Bloody exudate in pleural and peritoneal cavities; streptococci present in blood.

Rabbit B: weight, $1\frac{1}{2}$ kg.; temperature, 102°; leucocytes, 8,400. Received 2 c.c. of same culture subcutaneously in ear.

October 27, 4 P. M.—Temperature, 104°.8; leucocytes, 8,200.

October 28, 4 P. M.—Temperature, 103°.5; leucocytes, 23,400.

October 29, 4 P. M.—Temperature, 103°; leucocytes, 23,000.

Remained well.

EXPERIMENT III.

November 2, 4 P. M.—Rabbit A: weight, $2\frac{1}{4}$ kg.; temperature, 100°; leucocytes, 9,400. Received 2.5 c.c. of chloroform and 1 c.c. of streptococcus culture hypodermically in ear.

November 3, 4 P. M.—Temperature, 102°; leucocytes, 5,800.

November 4.—Died in the forenoon. Cultures from heart's blood positive.

Rabbit B: weight, 2¼ kg.; temperature, 101°; leucocytes, 10,100. Received 1 c.c of same culture as A hypodermically in ear.

November 3, 4 P. M.—Temperature, 104°; leucocytes, 22,800.

November 4, 4 P. M.—Temperature, 105°: 20,000.

November 5, 4 P. M.—Temperature, 102°; leucocytes, 21,000.

Rabbit recovered.

EXPERIMENT IV.

November 11, 4 P. M.—Rabbit A: weight, 2 kg.; temperature, 101°5; leucocytes, 11,400. Kept under chloroform for thirty minutes, but was not completely under. Received 2 c.c. of streptococcus culture.

November 12, 4 P. M.—Temperature, 104°; leucocytes, 24,200.

November 13, 4 P. M.—Temperature, 105°; leucocytes, 22,600.

November 14, 4 P. M.—Temperature, 105°; leucocytes, 16,500.

Had a marked erysipelas of ear. Leucocytes fell gradually, and animal died November 20. Streptococcus in blood.

Rabbit B: weight 2 kg.; temperature, 101°5; leucocytes, 13,100. Received 2 c.c. of same culture.

November 12, 4 P. M.—Temperature, 101°5; leucocytes, 18,100.

November 13, 4 P. M.—Temperature, 103°; leucocytes, 21,200.

November 14, 4 P. M.—Temperature, 103°; leucocytes, 20,900.

The leucocytes fell gradually, and the rabbit died November 22. Streptococcus found in blood.

EXPERIMENT V.

November 19, 4 P. M.—Rabbit A: weight 2 kg.; temperature, 102°; leucocytes, 18,200. Kept under chloroform thirty minutes. Received 2 c.c. of pneumococcus culture of low virulence.

November 20, 4 P. M.—Temperature, 105°; leucocytes, 20,200.

November 21, 4 P. M.—Temperature, 105°; leucocytes, 23,400.

November 23, 4 P. M.—Temperature, 104°; leucocytes, 15,800.

November 24, 4 P. M.—Temperature, 105°; leucocytes, 17,800.

November 25, 4 P. M.—Temperature, 102°5; leucocytes, 18,000.

November 27, 4 P. M.—Temperature, 102°; leucocytes, 18,000.

November 28, 4 P. M.—Temperature, 102°5; leucocytes, 25,000.

Recovered.

Rabbit B: weight, 2 kg.; temperature, 102°5; leucocytes, 14,300. Received same culture and dose as A.

November 20, 4 P. M —Temperature, 104°2; leucocytes, 19,200.

November 21, 4 P. M.—Temperature, 104°; leucocytes, 24,200.

November 23, 4 P. M.—Temperature, 103°5; leucocytes, 13,400.

November 24, 4 P. M.—Temperature, 104°; leucocytes, 13,600.

November 25, 4 P. M.—Temperature, 103°; leucocytes, 13,000.

November 27, 4 P. M.—Temperature, 102°5; leucocytes, 19,000.

November 28, 4 P. M.—Temperature, 103°; leucocytes, 16,000.

Rabbit recovered.

The results of the chloroform series are not unlike those obtained with alcohol and ether. The last experiment might have come out differently had Rabbit A been more fully anesthetized. Owing to certain accidents in the course of the chloroform series, the narcotic was employed very cautiously, and the rabbit was allowed to come out of its influence several times during the half-hour. It seems that to produce a decided effect it is necessary to employ enough of the narcotic chosen, to produce complete narcosis, even if that should last only a short time. And I have reason to believe that the longer the narcotization lasts, the more complete and the longer is the suspension of immunity.

It may be well to state here that in the foregoing experiments only comparative results were sought, and the complete recovery of all the control animals was not at all anticipated, since the infectious materials used in many instances were surely many times the lethal dose.

These experiments appear to show that the narcotics in question have a decidedly unfavorable effect on the resistance of rabbits to infections. It does not make any difference how the narcotic is administered. As long as the necessary quantity is absorbed by the system the results are the same. This might well serve to explain post-operative pneumonia, and the drunkard's predisposition to pneumonia, as also the especially severe character of the disease in such persons. The susceptibility of alcoholics to tuberculosis is also an established clinical fact.

Impressed with the idea that the number and quality of the leucocytes have a certain connection with immunity, it seemed desirable to make a series of careful leucocyte counts of drunkards' blood. The following observations have been made on inmates of the Washingtonian home, an institution conducted especially for the care of those addicted to the use of alcohol and other narcotics. I am greatly indebted to the management of that worthy institution for the privilege and especially to Drs. Smith and Goodsmith, of the house staff, for many courtesies.

TABLE I.

LEUCOCYTE COUNTS OF SIXTY ALCOHOLICS.

No.	Name	Age	Occupation	Steady Drinker No. Years	Periodical Drinker No. Years	Leucocyte Count
1	A. W. G.	43	Merchant	20		4,600
2	W. G. C.	40	Salesman		20	8,200
3	O. M.	44	R. R. employee		16	6,200
4	G. P. T.	43	Bartender	15		5,600
5	D. M.	52	Trav. salesman		25	4,200
6	T. R.	44	City employee	15		5,600
7	F. E. L.	35	Newspaper man	10		4,000
8	C. O. J.	37	Engineer	17		5,300
9	T. M.	34	Waiter	15		5,600
10	A. W.	44	Harness-maker		20	3,550
11	J. E. Q.	44	Waiter	25		2,100
12	P. M. I.	30	Letter-carrier	12		4,300
13	J. H. B.	30	Bookkeeper	12		5,400
14	G. E. C.	39	Board of Trade	20		4,000
15	E. M.	42	Lumberman	20		4,700
16	Erig. M.	32	Telegrapher		10	9,700
17	G. D.	52	Laborer	30		3,400
18	J. E. J.	32	Laborer	15		4,000
19	C. T. K.	46	Jeweler		18	9,750
20	G. F. G.	39	Grocer	12		5,400
21	G. E. C.	45	Newspaper man	25		4,600
22	S. P.	34	Laborer	10		5,050
23	M. C. M.	41	Tailor		20	6,200
24	P. T. M.	46	Solicitor	30		4,300
25	M. J. M.	24	Butcher		6	5,050
26	A. M.	53	Saloonkeeper	20		3,700
27	C. O. E.	31	Painter	12		6,500
28	A. M. L.	49	Bookkeeper	20		5,200
29	P. McE.	47	City employee	20		3,600
30	J. R.	37	Laborer	20		6,500
31	G. W. S.	40	Salesman	20		4,700
32	J. P. P.	61	Salesman		40	6,900
33	L. P. C.	37	Farmer	15		4,800
34	J. A. A.	31	Painter	12		4,700
35	A. W.	42	Barber	22		5,000
36	W. E. P.	42	R. R. employee	20		5,500
37	R. J. F.	49	Janitor		15	6,800
38	F. B.	41	Metal-worker	15		4,500
39	J. M.	36	Teamster		18	4,300
40	G. W. M.	45	Painter	18		3,800
41	F. T.	35	Actor	15		6,300
42	J. B.	50	Grocer	25		6,750
43	J. G. C. C.	31	Painter	12		5,800
44	F. U.	36	Bookbinder	10		4,850
45	J. D. C.	48	Trav. salesman	30		5,100
46	J. M.	32	Laborer	10		7,400
47	C. D.	44	Solicitor		20	6,300
48	J. E. M.	41	Woodworker	15		5,400
49	A. J.	30	Peddler	10		6,800
50	H. E. M.	42	Printer	22		4,600
51	F. E.	48	Clerk		10	8,000

TABLE I.—*Continued.*

No.	Name	Age	Occupation	Steady Drinker No. Years	Periodical Drinker No. Years	Leucocyte Count
52	J. T. C.	58	Painter		30	7,100
53	H. A.	62	Merchant		35	5,700
54	A. H.	40	Barber	20		8,000
55	W. W. H.	34	Coachman	10		6,000
56	T. R.	41	Teamster	18		5,300
57	R. T.	38	Grocer	15		6,200
58	J. S.	36	Tailor	12		5,000
59	C. A.	55	Merchant	25		4,900
60	P. O.	42	Plumber		20	5,600
						Average, 5,300

The average number of leucocytes for the individual is 5,300. The average normal number of leucocytes per cubic millimeter is, according to the best modern authorities, 7,500, which means a diminution of 2,200 in the average alcoholic. Of the individuals 92 per cent. fall below 7,500; 72 per cent. below 6,000; 44 per cent. below 5,000; 12 per cent. below 4,000, and 2 per cent. below 3,000; 8 per cent. have above the normal number.

Differential counts made in twenty-five individuals show no change in the ratio of the different forms of leucocytes:

TABLE II.

DIFFERENTIAL LEUCOCYTE COUNT.

No.	Polynuclear	Lymphocytes	Large Mononuclears	Eosinophiles	No.	Polynuclear	Lymphocytes	Large Mononuclears	Eosinophiles
1	75.0%	15.0%	10.0%	0.5%	15	66.0%	29.5%	4.0%	0.5%
2	57.0	30.0	11.5	1.5	16	74.0	20.0	6.0	...
3	72.0	23.0	4.0	1.0	17	82.0	12.0	6.0	...
4	80.0	15.0	3.0	2.0	18	66.0	25.0	8.5	0.5
5	63.5	24.0	10.0	2.5	19	72.0	16.5	9.5	1.5
6	75.0	17.0	8.0	...	20	67.5	23.5	7.5	1.5
7	84.0	11.0	5.0	...	21	77.5	15.0	6.0	1.5
8	77.0	15.5	6.5	1.0	22	71.0	19.0	10.0	...
9	63.5	26.5	8.0	2.0	23	76.0	18.5	4.5	1.0
10	72.0	22.0	6.0	...	24	79.0	13.5	6.0	1.5
11	72.0	15.0	8.0	5.0	25	69.0	19.0	11.5	0.5
12	67.0	22.5	7.5	3.0					
13	72.5	21.0	6.5	...	Av'ge	72.0	19.0	7.0	1.02
14	73.0	20.0	6.5	0.5					

All the blood specimens were taken at about 11 A. M.—that is, four hours after the regular breakfast hour, 7 A. M. To prove whether four hours was a sufficient interval, I made a number of counts at 6 and at 6:30 A. M. in the same individuals that I examined at 11 A. M., and found no marked difference in the number of leucocytes. According to von Limbeck, the number of leucocytes in healthy males at 11 A. M.—the same hour as my counts were made—is 7,660, making the difference between the normal and the number found by me still greater. It is interesting to note that there is an appreciable difference in the average leucocyte counts of the periodical and the steady drinker. The latter has 5,100, while the periodical drinker has 6,500—a difference of 1,400 leucocytes.

One might attempt to explain the foregoing observations by assuming that alcohol has an unfavorable effect upon the leucocytogenic centers (*i. e.*, bone marrow and lymphatic glands), so that in the habitual inebriate, in whom the leucocyte-producing tissues are constantly under the influence of the toxic agent, there is a smaller output of white blood corpuscles, while in the periodical drunkard the same tissues have a chance to recuperate between the periods of intoxication, and are therefore better able to produce leucocytes.

THE NUMERICAL RELATIONS OF CIRCULATING BACTERIA TO LEUCOCYTES.

To ascertain the numerical relationship between the circulating bacteria (pneumococci) and the leucocytes, cultures and leucocyte counts were made at the same time. These observations were carried on in conjunction with Dr. Rosenow, who made the counts of the colonies.

OBSERVATION I.

A rabbit etherized and infected twenty-four hours previously with pneumococcus has a temperature of 103°.5 F.; leucocytes, 24,000. Blood cultures made at the same time gave 168 colonies to the loop of blood, that being the average of twelve loops. Forty-eight hours later, before the rabbit died, the leucocyte count was 3,700, and the colonies per loop numbered 46,500 from an average of twelve loops.

OBSERVATION II.

A rabbit etherized and infected forty-eight hours previously with pneumococcus has a temperature of 105°, a leucocytosis of 17,000, and blood cultures made at the same time gave 139 colonies per loop from an average of twelve loops. Twenty-four hours later, immediately before the death of the animal, there was a leucocyte count of 1,160 and 142,900 colonies to the loop of blood from cultures made at the same time.

OBSERVATION III.

A rabbit sick from pneumococcus infection, with a leucocyte count of 27,000, gave only 38 colonies to the loop of blood from an average of twelve loops.

From these observations we may conclude that the presence of leucocytes in the circulation in large numbers limits the numbers of the circulating bacteria, but that as soon as the leucocytes diminish in number there is a rapid rise in the number of bacteria.

In the experiments with alcohol, ether, and chloroform, there were some rabbits that were narcotized, and that had about the same number of leucocytes as the control rabbits, shortly after a certain infection; but those treated with the narcotics either succumbed or did not resist the infection as well as the controls. Now, the question arises whether it is simply the hyperleucocytosis that protects the animal against certain poisons, or whether it also depends upon the quality (chemiotactic and phagocytic) of the individual corpuscles. From the several experiments given above, it would seem that the protection of the animal against various infections depends upon both the number and quality of the white blood corpuscles, otherwise, when both the narcotized and the control rabbit had the same leucocyte count, being infected with the same amount of culture and kept under the same conditions, why should only the former die? To test this possibility, I have undertaken to find out whether the narcotics exert any influence upon the phagocytic action of leucocytes.

In determining the phagocytic qualities of the cells, it was necessary to select some substance which they would take up and which could be easily recognized within the cell. I first thought of the trisulphide of arsenic, which was especially prepared by Besredka for his experiments described above. But this was abandoned because of the toxic properties of the drug. I then tried powdered charcoal, insoluble Prussian blue and carmine. The latter was finally selected, though it seemed to me that the charcoal and the blue were taken up more readily by the phagocytes. However, the color of those substances made it difficult to separate them from the cell granules and nuclei, especially when treated with acetic acid.

EXPERIMENT I.

Rabbit A received intraperitoneally 3 c.c. of an emulsion of carmine in distilled water by means of a Pasteur pipette. Twenty-four hours later some peritoneal exudate was withdrawn and examined fresh and in acetic acid. Carmine granules were found in about 20 per cent. of the leucocytes. Many of the phagocytes contained as much as ten granules of carmine. In certain fields of the microscope there were as many as 30 per cent. of the leucocytes containing red granules.

Rabbit B was etherized hypodermically and injected intraperitoneally with the same emulsion of carmine and the same amount as in Rabbit A. Twenty-four hours later the exudate from the peritoneum showed that only 5–6 per cent. of the leucocytes contained carmine granules.

EXPERIMENT II.

Rabbit A was injected intraperitoneally with carmine in the same manner as in the previous experiment. The peritoneal exudate was withdrawn twenty-four hours later, and on examination 14 per cent. of the leucocytes were found to contain granules of carmine. Some of them contained as many as eight and ten distinct granules.

Rabbit B was narcotized with alcohol hypodermically and received the same amount of carmine in the peritoneal cavity as Rabbit A. Twenty-four hours later some of the peritoneal exudate was withdrawn and examined as in the previous experiments. It was found that only six out of a hundred leucocytes contained carmine granules. In this experiment the rabbit received a second smaller dose of alcohol four hours after the first one, owing to the quick recovery of the animal from the effects of the first dose.

CHEMIOTACTIC INFLUENCE OF ALCOHOL ON LEUCOCYTES.

A capillary tube filled with alcohol was inserted subcutaneously in the ear of a rabbit, and another capillary tube filled with bouillon was inserted in the other ear. Twenty-four hours later the tubes were removed and examined under the microscope. The bouillon capillary was filled with leucocytes from the inserted end up to a considerable distance, while the alcohol capillary was absolutely free from leucocytes.

In a second experiment two capillary tubes—one containing alcohol and the other bouillon—were inserted subcutaneously in one ear of a rabbit, only 2 cm. apart. When removed twenty-four hours later and examined under the microscope, the same phenomenon as in the first experiment was observed—*i. e.*, the bouillon tube was filled at the inserted end with leucocytes, while the one containing the alcohol was absolutely free from leucocytes.

From the latter experiments we may conclude that there is a negative chemiotaxis between the leucocytes and alcohol, and this may help to explain why the leucocytes do not appear in as great numbers in infected animals that have also been alcoholized as in those that were not; and those leucocytes that do circulate in the blood stream which contains alcohol were not able to perform their phagocytic function so well, as shown in some of the above experiments. This will perhaps also explain the difference in the leucocyte counts found in the periodical and steady drinkers.

It might be reasonable to suppose that ether and chloroform would give similar results. I have omitted to test the latter narcotics, because they are so easily evaporated, and the results could not have been considered conclusive.

In summing up the results of this work, the following conclusions may be drawn:

1. That alcohol, ether, and chloroform have a decidedly detrimental influence on the natural defenses against infection, and that this lowering or suspension of the resisting power of the

animal is not due to any apparent organic lesions, since no changes in any of the vital organs were discoverable in any of the animals, except such as were caused by the infectious material employed.

2. The narcotics appear to affect directly the substance or substances which inhibit the growth and toxic action of bacteria in the normal animal, and these substances are either the leucocytes themselves or something derived from them or both. Snel has shown in his work that alcohol and ether suspend also conferred immunity against a specific microbe.

3. The period of detrimental action of the narcotic depends largely on the amount administered, the depth of narcosis, and the rapidity of its elimination from the system. Some of the narcotized animals that were employed in other experiments with infectious material twenty-four hours later (*i. e.*, after narcotization) fared as well as the new rabbits.

There are several other questions to be settled in connection with this theme, but they will be left for a separate study.

In closing, I wish to extend my sincere thanks to Professor Hektoen for numerous valuable suggestions and courtesies. I wish to thank also Dr. Rosenow for many kindnesses and favors.

REFERENCES.

ARNOLD. *Münch. med. Wchnschr.*, 1902, 49, p. 1945.
BESREDKA. *Annales de l'Inst. Pasteur*, 1899, 13, pp. 49, 209, 465.
BORDET. *Ibid.*, 1903, 17, p. 161; *ibid.*, 1895, 9, p. 462; *ibid.*, 1896, 10, p. 104.
BRINCKERHOFF AND TYZZER. *Jour. Med. Research*, 1902, 7, p. 191.
CANTACUZÈNE. *Annales de l'Inst. Pasteur*, 1901, 12, p. 273.
GRÜNBAUM. *Lancet*, 1903, p. 775.
HIRSCHFELD. *Virchow's Arch.*, 1901, 166, p. 195.
LINDEMANN. *Centralbl. f. allg. Path. u. Anat.*, 1898, 9, p. 442.
LEVADITI. *Annales de l'Inst. Pasteur*, 1903, 17, p. 187.
METCHNIKOFF. *L'immunité dans les maladies infectieuses.*
MARKL. *Ztschr. f. Hyg. u. Infectionskr.*, 1903, 42, p. 244.
MENDELSON. *Vratch*, 1903, 10, p. 130.
SALIMBENI. *Annales de l'Inst. Pasteur*, 1898, 12, p. 192.
SNEL. *Berl. klin. Wchnschr.*, 1903, 10, p. 212.
STEWART. *Jour. Med. Research*, 1902, 8, p. 268.
WASSERMANN. *Ztschr. f. Hyg. u. Infectionskr.*, 1901, 37, p. 173
WILLSON. *Jour. Amer. Med. Assn.*, 1903, p. 1191.